Exhibit I

Table A–II–1
PHARMACOKINETIC DATA (*Continued*)

AVAILABILITY (ORAL) (%)	URINARY EXCRETION (%)	BOUND IN PLASMA (%)	CLEARANCE ($ml \cdot min^{-1} \cdot kg^{-1}$)	VOL. DIST. (*liters/kg*)	HALF-LIFE (*hours*)	EFFECTIVE CONCENTRATIONS	TOXIC CONCENTRATIONS
OMEPRAZOLE							
53 ± 29[a] ↑ Aged, Cirr	Negligible	95[b]	7.5 ± 2.7[c,d] ↓ Aged, Cirr ⟷ Urem	0.34 ± 0.09[a] ⟷ Aged, Cirr	0.7 ± 0.5[c] ↑ Aged, Cirr ⟷ Urem	—	—

[a]Increases upon multiple dosing to 70 ± 26%.
[b]Blood-to-plasma concentration ratio = 0.58.
[c]Substrate for CYP2C19 and CYP3A. Patients deficient in CYP2C19 exhibit a clearance of 1.0 ± 0.2 $ml \cdot min^{-1} \cdot kg^{-1}$ and a half-life of 2.7 ± 0.7 hours.
[d]Decreases upon multiple dosing.

Reference: Chang, M., Tybring, G., Dahl, M.-L., Götharson, E., Sagar, M., Seensalu, R., and Bertilsson, L. Interphenotype differences in disposition and effect on gastrin levels of omeprazole—suitability of omeprazole as a probe for CYP2C19. *Br. J. Clin. Pharmacol.*, 1995, *39*:511–518.

ONDANSETRON							
62 ± 15[a] ↑ Aged, Cirr, Fem	5	73 ± 2[b]	5.9 ± 2.6 ↓ Aged, Cirr, Fem ↑ Child	1.9 ± 0.5 ⟷ Aged, Cirr	3.5 ± 1.2 ↑ Aged, Cirr ↓ Child	—	—

[a]In 25 cancer patients, 62 ± 10 years, $F = 86 \pm 26\%$.
[b]Blood-to-plasma concentration ratio = 0.83.

Reference: Roila, F., and Del Favero, A. Ondansetron clinical pharmacokinetics. *Clin. Pharmacokinet.*, 1995, *29*:95–109.

PENICILLIN V							
33	46 ± 4	92.2 ± 0.6	6.1 ± 1.7	0.33 ± 0.09[a]	0.4–0.7 ↑ Urem	*See* Chapter 45	—

[a]V_{area}.

Reference: Dittert, L.W., Griffen, W.O., Jr., LaPiana, J.C., Shainfeld, F.J., and Doluisio, J.T. Pharmacokinetic interpretation of penicillin levels in serum and urine after intravenous administration. *Antimicrob. Agents Chemother.*, 1969, *9*:42–48.

OXAPROZIN							
95–100	Negligible	>99.5[a] ↓ Urem ⟷ Aged, CHF, Fem	0.028–0.042[b] ⟷ Aged, CHF, Cirr, Fem	0.14–0.24[b] ⟷ Aged, CHF, Cirr	21–25[c] ⟷ Aged, CHF, Cirr, Fem	—	—

[a]Decreases with increasing concentrations.
[b]Mean total clearance and volume of distribution for 300- to 1200-mg doses. Unbound clearance is constant (about 40 $ml \cdot min^{-1} \cdot kg^{-1}$) over this dose range.
[c]Accumulation half-life; longer, 60-hour, terminal half-life is not consistent with time to achieve steady-state.

Reference: Todd, P.A., and Brogden, R.N. Oxaprozin: A preliminary review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs*, 1986. *32*:291–312.

97 ± 11	<1	98.8 ± 1.8 ↑ Urem, Alb ⟷ Aged, AVH, Cirr	1.05 ± 0.36 ↑ HTh, Smk, Urem[a] ⟷ LTh, Aged, AVH, Cirr	0.60 ± 0.20 ↑ Urem ⟷ Aged. AVH. Cirr	8.0 ± 2.4 ↑ Urem, Neo ↓ HTh ⟷ Aged, AVH, Cirr, LTh, Preg	—	—

[a]*CL/F* of unbound drug is unchanged in uremia.

Reference: Sonne, J., Loft, S., Dossing, M., Vollmer-Larsen, A., Olesen, K.L., Victor, M., Andreasen, F. and Andreasen, P.B. Bioavailability and pharmacokinetics of oxazepam. *Eur. J. Clin. Pharmacol.*, 1988, *35*:385–389.

Low	5 ± 2	95–98[a]	5.5 ± 3.5[b,c] ⟷ Child	2.0 ± 1.2[b] ⟷ Child	3 ± 1[d]	—	—

[a]A recent report suggests binding to dialysis filtration devices leads to overestimates of 88% protein-bound.
[b]Saturable distribution, which would also appear as saturable clearance, has been suggested.
[c]CYP2C8 and CYP3A4 substrate.
[d]Average accumulation half-life. Longer terminal half-lives, up to 30 hours have been reported.

Reference: Sonnichsen, D.S., and Relling, M.V. Clinical pharmacokinetics of paclitaxel. *Clin. Pharmacokinet.*, 1994, *27*:256–269.

—	67 ± 18 ⟷ CPBS	7 ± 2 ⟷ Neo, Fem, Preg, Urem	1.8 ± 0.4 ↓ Aged, Urem ⟷ Cirr, CPBS	0.26 ± 0.07 ⟷ Aged. Urem. CPBS ↑ Cirr	2.3 ± 0.4 ↑ Aged, Urem, Cirr ⟷ CPBS	0.25 ± 0.07 μg/ml[a] 0.40 μg/ml[b]	—

[a]50% decrease in twitch tension.
[b]95% decrease in twitch tension.

Reference: Shanks, C.A. Pharmacokinetics of the nondepolarizing neuromuscular relaxants applied to calculation of bolus and infusion dosage regimens. *Anesthesiology* 1986, *64*:72–86.

Dose-dependent	<2	95	8.6 ± 3.2[a,b] ↓ Cirr, Aged	17 ± 10[c]	17 ± 3[d] ↑ Cirr, Aged	—	—

[a]*CL/F* for multiple dosing data in extensive metabolizers. Single dose data significantly higher. In poor metabolizers *CL/F* = 5.0 ± 2.1 ml · min^{-1} · kg^{-1} for multiple dosing.
[b]CYP2D6 substrate which exhibits saturable metabolism.
[c]V_{ss}/F.
[d]For multiple dosing in extensive metabolizers. In poor metabolizers $t_{1/2}$ = 41 ± 8 hours.

Reference: Sindrup, S.H., Brosen, K., Gram, L.F., Hallas, J., Skjelbo, E., Allen, A., Allen, G.D., Cooper, S.M., Mellows, G., Tasker, T.C.G., and Zussman, B.D. The relationship between paroxetine and the sparteine oxidation polymorphism. *Clin. Pharmacol. Ther.* 1992, *51*:278–287.

Key: Adult = adults; Aged = aged; Alb = hypoalbuminemia; Arth = arthritis; Atr Fib = atrial fibrillation; AUC = area under the curve; AVH = acute viral hepatitis; Burn = burn patients; CAD = coronary artery disease; Celiac = celiac disease; CF = cystic fibrosis; CHF = congestive heart failure; Child = children; Cirr = cirrhosis; COPD = chronic obstructive pulmonary disease; CF = cor pulmonale; CPBS = cardiopulmonary bypass surgery; CRI = chronic respiratory insufficiency; Crohn = Crohn's disease; Cush = Cushing's syndrome; Epilep = epileptic; Fem = female; Hep = Hepatitis; HL = hyperlipoproteinemia; HTh = hyperthyroid; Inflam = inflammation; LTh = hypothyroid; MI = myocardial infarction; Neo = neonate; NS = nephrotic syndrome; Obes = obese; Pneu = pneumonia; Preg = pregnant; Prem = premature; RA = rheumatoid arthritis; Smk = smoking; Tach = ventricular tachycardia; Ulcer = ulcer patients; Urem = uremia

nomas of the breast, the bladder, and the male and female reproductive systems.

Clinical Toxicities. The clinical toxicity of vincristine is mostly neurological, as described above. The more severe neurological manifestations may be avoided or reversed by either suspending therapy or reducing the dosage upon occurrence of motor dysfunction. Severe constipation, sometimes resulting in colicky abdominal pain and obstruction, may be prevented by a prophylactic program of laxatives and hydrophilic agents and is usually a problem only with doses above 2 mg/m^2.

Alopecia occurs in about 20% of patients given vincristine; however, it is always reversible, frequently without cessation of therapy. Although less common than with vinblastine, leukopenia may occur with vincristine, and thrombocytopenia, anemia, polyuria, dysuria, fever, and gastrointestinal symptoms have been reported occasionally. Ischemic cardiac toxicity has been reported. The syndrome of hyponatremia associated with high urinary concentration of Na^+ and inappropriate secretion of antidiuretic hormone occasionally has been observed during vincristine therapy. In view of the rapid action of the vinca alkaloids, it is advisable to take appropriate precautions to prevent the complication of hyperuricemia. This can be accomplished by the administration of allopurinol (*see* above).

Vinorelbine

Vinorelbine (NAVELBINE) is administered in normal saline as an intravenous infusion of 30 mg/m^2 given over 6 to 10 minutes. It is initially given every week until progression of disease or dose-limiting toxicity when used alone. When used with cisplatin for the treatment of non-small cell lung carcinoma, it is given less frequently (every 4 to 6 weeks). Its primary toxicity is granulocytopenia, with only modest thrombocytopenia and less neurotoxicity than other vinca alkaloids. In experimental studies, it has been given in an oral capsule, but bioavailability is only 30% to 40% (Fumoleau *et al.*, 1993).

Paclitaxel

This compound, first isolated from the bark of the Western yew tree in 1971 (Wani *et al.*, 1971), exhibits unique pharmacological actions as an inhibitor of mitosis, differing from the vinca alkaloids and colchicine derivatives in that it promotes rather than inhibits microtubule formation. Following its introduction into clinical trial, the drug was approved for treatment of cisplatin-refractory ovarian cancer in 1992 (Rowinsky *et al.*, 1993; Rowinsky and Donehower, 1995) and has promising activity against cancers of the breast, lung, esophagus, and head and neck. The optimal dose, schedule, and use in drug combinations are incompletely understood.

Chemistry. Paclitaxel (TAXOL) is a diterpenoid compound that contains a complex taxane ring as its nucleus (Figure 51–13). The side chain linked to the taxane ring at carbon 13 is essential for its

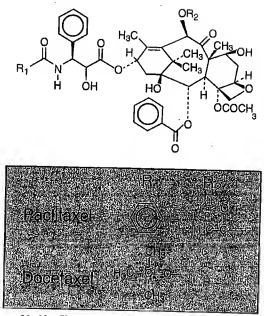

Figure 51–13. Chemical structures of paclitaxel (TAXOL) and its more potent analog, docetaxel (TAXOTERE).

antitumor activity. Modification of the side chain has led to identification of a more potent analog, docetaxel (TAXOTERE) (Figure 51–13), which has clinical activity against breast and ovarian cancers. Originally purified as the parent molecule from yew bark, paclitaxel can now be obtained for commercial purposes by semisynthesis from 10-desacetylbaccatin, a precursor found in yew leaves. It also has been successfully synthesized (Nicolau *et al.*, 1994) from simple off-the-shelf reagents in a complex series of reactions. The molecule has very limited solubility and must be administered in a vehicle of 50% ethanol and 50% polyethoxylated castor oil (Cremophor EL), a formation likely responsible for a high rate of hypersensitivity reactions in patients not protected with both an H_1 antihistamine agent such as diphenhydramine, an H_2 antihistamine agent such as cimetidine (*see* Chapter 25), and a corticosteroid such as dexamethasone (*see* Chapter 59).

Mechanism of Action. Interest in paclitaxel was stimulated by the finding that the drug possessed the unique ability to promote microtubule formation at cold temperatures and in the absence of GTP. It binds specifically to the β-tubulin subunit of microtubules and appears to antagonize the disassembly of this key cytoskeletal protein, with the result that bundles of microtubules and aberrant structures derived from microtubules appear in paclitaxel-treated cells. Arrest in mitosis follows. Cell killing is dependent on both drug concentrations and duration of cell exposure. Drugs that block the progression of cells through DNA synthesis and into mitosis antagonize the toxic effects of paclitaxel. Schedules for its optimal use in combination

with other drugs, including doxorubicin and cisplatin, have not yet been defined, although the sequence of cisplatin preceding paclitaxel produces greater toxicity than the opposite schedule (Rowinsky *et al.*, 1991). Doxorubicin preceding paclitaxel leads to greater toxicity and less *in vitro* therapeutic effect than the opposite sequence.

In cultured tumor cells, resistance to paclitaxel is associated in some lines with increased expression of the *mdr*-1 gene and its product, the P-glycoprotein; other resistant cells have tubulin mutations, and these latter cells may display heightened sensitivity to vinca alkaloids (Cabral, 1983). The basis of clinical drug resistance is not known.

Absorption, Fate, and Excretion. Paclitaxel is administered as a 3-hour or 24-hour infusion. Longer infusions (96 hours) have yielded high response rates in breast cancer patients in preliminary trials (Wilson *et al.*, 1994). The drug undergoes intensive P450-mediated hepatic metabolism (isoenzymes CYP3A and CYP2C), and less than 10% of a dose is excreted in the urine intact. The primary metabolite identified thus far is 6-OH paclitaxel, but multiple additional products are found in urine and plasma (Cresteil *et al.*, 1994).

Paclitaxel clearance is saturable and decreases with increasing dose or dose rate (Table 51–3). In studies of 96-hour infusion of 35 mg/m^2 per day, the presence of hepatic metastases greater than 2 cm in diameter decreased clearance and led to high drug levels in plasma and greater myelosuppression. Paclitaxel disappears from the plasma compartment with half-lives of approximately 0.2, 2, and 20 hours. The critical plasma concentration for inhibiting bone marrow elements depends on duration of exposure but likely lies in the range of 0.01 to 0.1 μM (Huizing *et al.*, 1993).

While precise guidelines for dose reduction in patients with abnormal hepatic function have not been established, 50% to 75% doses should be used in the presence of hepatic metastases greater than 2 cm in size or in patients with abnormal serum bilirubin.

Therapeutic Uses. Paclitaxel has undergone initial phases of testing in patients with metastatic ovarian and breast cancer; it has significant activity in both diseases, including diseases in patients that have progressed on standard primary combination regimens. Response rates in relapsed patients range from 20% to 50%, depending on the treatment history and the regimen employed. Early trials indicate significant response rates in lung, head and neck, esophageal, and bladder carcinomas as well (Arbuck *et al.*, 1993). The optimal schedule of paclitaxel administration, alone or in combination with other drugs, has not been defined.

Clinical Toxicities. Paclitaxel exerts its primary toxic effects on the bone marrow. Neutropenia usually occurs 8 to 11 days after a dose and reverses rapidly by days 15 to 21. Used with G-CSF, doses as high as 250 mg/m^2 over 24 hours are well tolerated, and peripheral neuropathy becomes dose-limiting (Kohn *et al.*, 1994). Many patients experience myalgias for several days after receiving paclitaxel. In high-dose schedules, a stocking–glove sensory neuropathy can be disabling, particularly in patients with underlying diabetic or alcoholic neuropathy. Mucositis is prominent in 72- or 96-hour infusions.

Hypersensitivity reactions occurred in patients receiving paclitaxel infusions of short duration (1 to 6 hours) but have largely been averted by pretreatment with dexamethasone, diphenhydramine, and cimetidine, as noted above. Premedication is not necessary with 96-hour infusion. Many patients experience asymptomatic bradycardia, and occasional episodes of silent ventricular tachycardia also occur and resolve spontaneously during 3- or 24-hour infusions.

EPIPODOPHYLLOTOXINS

Podophyllotoxin, extracted from the mandrake plant (mayapple; *Podophyllum peltatum*), was used as a folk remedy by the American Indians and early colonists for its emetic, cathartic, and anthelmintic effects. Two semisynthetic glycosides of the active principle, podophyllotoxin, have been developed that show significant therapeutic activity in several human neoplasms, including pediatric leukemia, small cell carcinomas of the lung, testicular tumors, Hodgkin's disease, and large cell lymphomas. These derivatives are referred to as *etoposide* (VP-16-213) and *teniposide* (VM-26). Although podophyllotoxin binds to tubulin at a site distinct from that for interaction with the vinca alkaloids, etoposide and teniposide have no effect on microtubular structure or function at usual concentrations. (For review of the epipodophyllotoxins, *see* Pommier *et al.*, 1995).

Table 51–3
Paclitaxel Clearance as a Function of Drug Infusion Rate

SCHEDULE	INFUSION RATE, mg/m^2 PER HOUR	PLASMA CLEARANCE, ml/min per m^2
1. 175 mg/m^2 over 3 hours	58	212
2. 175 mg/m^2 over 24 hours	7	393
3. 140 mg/m^2 over 96 hours	1.5	471